UNITED STATES DEPARTMENT OF COMMER
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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/455,975	05/31/95	RUBIN J	40399/299/I

18M2/0411

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1801	8

DATE MAILED: 04/11/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 10 December 1996

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days~~, ~~whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 21, 23 - 37 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from considerat

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 21, 23 - 37 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirem

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disappro

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

Serial Number: 08/455,975
Art Unit: 1801

Part III DETAILED ACTION

1. Applicant's response filed 10 December 1996 has been received. Applicant should note that the amendment to the claims has been entered, therefore, claim 22 has been canceled, claims 21, 23-28 have been amended and claims 30-37 have been added and are pending in the instant application. No other amendments filed on 10 December 1996 have been officially entered at this time for the reasons listed below under *Specification*.

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior office action.

4. Applicant's arguments filed 10 December 1996 have been fully considered but they are not deemed to be persuasive.

Specification

5. A substitute specification was requested in the instant application because of the numerous amendments which needed to be made to the specification. Applicant's

have provided a substitute specification with some of the amendments included, yet also include 7 **more** pages of amendments. As stated in the previous Office action, the numerous amendments which have been submitted result in a specification with potential errors as well as a copy which is not easily readable for the printer (at the time of allowance and issue). In addition, the filing of a substitute specification requires the submission of a hand corrected copy of the portions of the original specification which are being added or deleted **with additions being underlined and deletions being bracketed**. In addition, a statement that the substitute specification contains no new matter and that the substitute specification includes the same changes as are indicated in the hand corrected original specification is required. Such statement must be a verified statement if made by a person not registered to practice before the Office. See MPEP § 714.20.

Response to Amendment

6. Applicant's inclusion and update of the history of the parent application which the instant application claims priority is appreciated. However, since the substitute specification and the amendments thereto were not entered, the required substitute specification should include this information along with all of the other amendments submitted with paper #7.

Claim Rejections - 35 USC § 112

7. Claims 21, 23, 25-28 and dependent claims 24, 29 and 30-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating epithelial cell growth with KGF and KGF polypeptides which is truncated within the region of amino acids 32-78, does not reasonably provide enablement for "treating a condition by specific stimulation of epithelial cell growth" with KGF or for "portions thereof" as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the instant claims.

The specification does not provide enablement for the invention which is commensurate in scope with claims to "treating a condition". The specification provides a protein, keratinocyte growth factor (KGF), which stimulates epithelial cells specifically (i.e. does not stimulate fibroblast cells). The specification is also enabled for using this protein (and/or pharmaceutical compositions) for stimulating epithelial cell growth, either *in vivo* or *in vitro*. However, the specification fails to enable a method for treating a generic condition by "specific stimulation of epithelial cell growth". The claims currently encompass treating any condition, from obesity to pregnancy, for which the current specification is clearly not enabled. The specification does not identify which conditions would benefit from epithelial cell stimulation, and one of ordinary skill in the art would not be able to reasonably be able to predict all of the conditions which could benefit from KGF administration. Claims to a method of

stimulating epithelial cell growth are supported by the specification as filed and would provide the breadth necessary to encompass use of KGF for stimulating epithelial cell growth in any condition for which it is administered. Dependent claims could also further limit the method for use in patient and wherein the stimulation is at a wound site, etc. However, the claims as currently presented are not commensurate in scope with the instant specification as indicated above. (It is noted that the claims were amended to encompass any condition, therefore, Applicant's amendment necessitated this new ground of rejection.)

Claim 27 is also a method of treating a condition, even though "by specific inhibition of epithelial cell growth", and is not enabled for the same reasons as listed above.

The specification teaches a keratinocyte growth factor (KGF) of 194 amino acids in length and DNA encoding said KGF. The specification also teaches that the first 31 amino acids are a signal sequence that is cleaved in the mature protein and that amino acids 32-78 confer epithelial cell specificity to the protein. However, the specification does not provide support for any portion of a KGF polypeptide, having ***preferential mitogenic activity on cells of epithelial origin.*** Two separate issues are raised by the wording of the claim. First, the language of a portion of a KGF polypeptide having preferential mitogenic activity does not give any structure to the amino acid sequence which is necessary for this preferential activity. This would include any fragment amino acids which stimulate preferential mitogenic activity. There is no support in the

specification that any portion from KGF would encode the preferential mitogenic activity of a KGF polypeptide, and it would required undue experimentation to determine how the amino acids could be arranged in order to facilitate preferential mitogenic activity. Furthermore, the claim must recite sufficient elements necessary for enablement of the claimed invention. In the instant case, there is evidence in the specification that amino acids 32-78 are ***responsible*** for conferring mitogenic specificity to the protein, the specification does not teach which other portions are necessary for mitogenic activity on epithelial cells or that portions of KGF which do not include these amino acids would possess preferential mitogenic activity for epithelial cells. Claim 31 is also not enabled for the same reasons in that the KGF polypeptide "comprises amino acids 65-156 and 162-189 of Figure 7". This claim does not recite sufficient elements necessary for enablement of the claimed invention, nor does the specification provide support that only amino acids 65-156 and 162-189 are required for stimulation of epithelial cells. It would require undue experimentation to determine which other amino acids are required for activity except for a KGF which comprises the amino acid sequence of Figure 7 or a KGF polypeptides which is truncated within the region of amino acids 32-78, which are enabled by the instant specification. Therefore, it would require undue experimentation for one of ordinary skill in the art to determine which portions of KGF would confer preferential mitogenic activity for epithelial cells, absent clear and convincing evidence to the contrary.

Claim 32 is not enabled for a KGF polypeptide encoded by a DNA which hybridizes to the DNA of Figures 6 and 7, because the DNA which hybridizes does not necessarily encode a protein, nor is it predictive which DNAs that meet the structural limitations (i.e. hybridizing) would also meet the functional limitations (i.e. encoding a protein which a particular biological activity) of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim. The claim encompasses a DNA which encodes KGF, a DNA which codes for substitutions, deletions, and insertions, as well as fragments, and, due to the possibility of frameshifts in polynucleotides, also encompasses polypeptides with virtually no amino acid similarity to KGF. The specification does not disclose which mutations can be made in KGF such that it retains biological activity, nor does it teach the critical amino acids (except for amino acids 32-78) or domains which are critical for its activity. Since there is a lack of sufficient guidance in the specification to determine which amino acid substitutions or alterations would produce a biologically active KGF or any working examples of any such variants and because the state of the art suggests that the effects of an alteration in protein sequence are unpredictable, undue experimentation would be required to determine which DNAs which hybridize to DNA encoding KGF would also encode a functional protein that could be used in the claimed methods, absent clear and convincing evidence to the contrary.

8. Claim 32 is rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 32 attempts to define the protein used in the method by the DNA encoding the protein, however, this does not further limit the protein. For example, a serine residue encoded by TCT or TCC or TCA or TCG is still the same serine residue and therefore claiming a serine and then claiming a serine encoded by a particular nucleic acid sequence would not further limit the subject matter of the previous claim. Furthermore, (a) and (b) are duplicative of each other because the protein encoded by the DNA of Figure 7 is necessarily the same protein as that which is encoded by the coding region of Figure 7 since the non-coding region does not provide any of the amino acids of the protein.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then

the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 4PM.

The fax phone number for this Group is (703) 308-0294. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christine Saoud, Ph.D.
April 9, 1997
CA

VASU S. JAGANNATHAN
PRIMARY EXAMINER
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